AWARD NUMBER: W81XWH-16-C-0188

TITLE: Tesamorelin Therapy to Enhance Axonal Regeneration, Minimize Muscle Atrophy and Improve Functional Outcomes Following Peripheral Nerve Injury and Repair

PRINCIPAL INVESTIGATOR: Jaimie T. Shores, MD

CONTRACTING ORGANIZATION: Johns Hopkins University, Baltimore, MD 21205

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6. AUTHOR(S)
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13. SUPPLEMENTARY NOTES

14. ABSTRACT

We are currently completing the set-up phase for this study. We have hired and trained all necessary staff. We have finalized drug distribution plans with Theratechnologies and the JHH research pharmacy. We have finalized our data management plan with REDCap and our biostatistician. We have received IRB approval from JHU IRB and IRB waivers from our primary recruitment sites (Union Memorial Hospital and University of Maryland Medical Center/Shock Trauma). The final step with regards to study set up prior to beginning recruitment will be to receive HRPO approval.

15. SUBJECT TERMS
IRB, FDA IND exemption, HRPO, study set-up phase

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
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Unclassified	Unclassified	Unclassified	Unclassified	11	19b. TELEPHONE NUMBER *(include area code)*

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1. **INTRODUCTION:** This study is a randomized, double-blinded, placebo-controlled clinical trial with the primary aim of assessing the efficacy of tesamorelin for peripheral nerve injuries. Patients with ulnar nerve lacerations at the wrist, repaired in a primary fashion, will be eligible for enrolment. Subject recruitment will take place primarily at Johns Hopkins Hospital, Union Memorial Hospital (Curtis National Hand Center), University of Maryland Medical Center/Shock Trauma, and Walter Reed National Military Medical Center. Subject follow up and outcome measurements will take place at Johns Hopkin Hospital. We plan to enroll 36 subjects over 4 years. At the end of the study, if tesamorelin is found to be efficacious, limited off-label use may be justified. Theratechnologies will then pursue a larger Phase 3 clinical trial aimed at achieving FDA-approval for tesamorelin to become the first drug indicated for treatment of peripheral nerve injuries.
2. **KEYWORDS:** Tesamorelin, peripheral nerve injury, peripheral nerve regeneration, Phase 2 clinical trial, motor recovery, sensory recovery.
3. **ACCOMPLISHMENTS:**

- **What were the major goals of the project?**

Below is a table listing the goals of the study as listed in the statement of work for Year 1, including the timeline as initially anticipated. Of note, we initially anticipated beginning patient recruitment in Year 1; however, initiation of patient recruitment has been delayed by the need for more time than anticipated for study set-up.

	Timeline	**Completed**
Major Task 1: Study Set Up	Months	
Coordinate with Theratechnologies for material transfer agreements	1-3	Yes
Complete Investigational New Drug (IND) application to the U.S. Food and Drug Administration	1-3	Yes
Refine eligibility criteria, exclusion criteria, screening protocol	1-3	Yes
Finalize consent form & human subjects protocol	1-3	Yes
Finalize assessment measurements	1-4	Yes
Coordinate with Sites for IRB** protocol submission	1-3	Yes
Coordinate with Sites for UMH (Means) and UMMC (Pensy) IRB** review	1-6	Yes
Coordinate with Sites for WR IRB** review (ORP/HRPO)	1-6	Pending
Submit amendments, adverse events and protocol deviations as needed	As needed	NA
Coordinate with Sites for annual IRB report for continuing review	Annually	NA
Milestone Achieved: FDA IND approval	3	Yes

*Milestone Achieved: Local IRB** approval at JHH, CNHC, UMMC/ST*	3, 4	Yes (waived at CNHC and UMMC/STC
*Milestone Achieved: HRPO*** approval for all protocols and local IRB**	6	Pending
Major Task 2: Coordinate Study Staff for Clinical Trials		
Coordinate for space allocation for new staff	1-3	Yes
Milestone Achieved: Study space allocated	2-3	Yes
Coordinate with Sites for job descriptions design	1-4	Yes
Advertise and interview for project related staff	1-4	Yes
Train/orient newly hired staff	4-6	Yes
Milestone Achieved: Research staff hired/trained	3-6	Yes

- **What was accomplished under these goals?**

The primary goal for Year 1 was to set up the study. All of the aims pertaining to study set-up, other than HRPO approval, have been achieved (see above table). Of note, we also anticipated beginning study enrollment in Year 1. However, this goal has been delayed by the need for more time than expected for study set-up. Unanticipated hurdles and delays were encountered for all aspects of the study set-up, including negotiating a material transfer agreement with Theratechnologies, identifying and hiring qualified study personnel, FDA IND clearance, and IRB clearance. However, we have now cleared all of hurdles pertaining to study set-up, other than HRPO approval, and we anticipate beginning subject enrollment in the next 2 months.

- **What opportunities for training and professional development has the project provided?**

Our Clinical Coordinator, Ala Elhelali, recently completed her PhD in clinical research and is using this opportunity to deepen her understanding of clinical research and gain experience in implementing a level 1 clinical trial. She has already gained tremendous insights by familiarizing herself with the protocol and helping set the stage for patient recruitment. She is approaching her position as a post-doctoral fellowship and ultimately plans to pursue a career in academia.

- **How were the results disseminated to communities of interest?**

We have yet to obtain results. The study results will remain blinded until the end of the study (Year 4).

- **What do you plan to do during the next reporting period to accomplish the goals**

During the next reporting period, we plan to obtain HRPO approval and begin enrolling subjects.

4. **IMPACT:**

- **What was the impact on the development of the principal discipline(s) of the project?**

Nothing to report.

- **What was the impact on other disciplines?**

Nothing to report.

- **What was the impact on technology transfer?**

Nothing to report.

- **What was the impact on society beyond science and technology?**

Nothing to report.

5. **CHANGES/PROBLEMS:**

- **Changes in approach and reasons for change**

There were no significant changes in approach other than some changes to personnel, which are detailed below under 'changes that had a significant impact on expenditures'

- **Actual or anticipated problems or delays and actions or plans to resolve them**

We experienced a number of unexpected delays in study set up which have delayed the initiation of subject enrollment. The most qualified candidates for the study coordinator and research technician positions applied from abroad and are not U.S. citizens. As such, the amount of time needed for them to come to Baltimore and commence work on the study was longer than expected. This issue has been resolved, as the research technician began work in early October and the clinical coordinator will begin in the next 2 weeks. The process of negotiating a material transfer agreement between Theratechnologies and JHU was also more time intensive and difficult than expected, which delayed subsequent stages of the set up. The IRB approval process took longer than expected, but has now been completed, with only HRPO approval remaining.

- **Changes that had a significant impact on expenditures**

A detailed request for budget adjustments, including rationale, was submitted last month. This document is attached under Appendices.

- **Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents**

Nothing to report

6. **PRODUCTS:**

- **Publications, conference papers, and presentations**

Nothing to report

- **Journal publications**

Nothing to report

- **Books or other non-periodical, one-time publications.**

Nothing to report

- **Other publications, conference papers, and presentations.**

Nothing to report

- **Website(s) or other Internet site(s)**

Nothing to report

- **Technologies or techniques**

Nothing to report

- **Inventions, patent applications, and/or licenses**

Nothing to report

- **Other Products**

Nothing to report

7. **PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS**

- **What individuals have worked on the project?**

Example:

Name:	*Jaimie Shores*
Project Role:	*PI*
Researcher Identifier (e.g. ORCID ID):	*1234567*
Nearest person month worked:	*1.8*
Contribution to Project:	*Dr. Shores has worked on all aspects of study set up*
Funding Support:	

- **Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?**

Sami Tuffaha, MD (Co-I) has the following recently funded grants:

Title: IGF-1 Nanoparticles to Improve Functional Recovery after Peripheral Nerve Injury
Sponsor: Plastic Surgery Foundation
Total Direct Cost: $50,000
Role: Co-Investigator (PI: Philip Hanwright)
(Jul 2016- June 2017)
Research fellowship salary support for Philip Hanwright.

Title: Locally-Delivered IGF-1 Nanoparticle Therapy for Peripheral Nerve Injury
Sponsor: American Foundation for Surgery of the Hand (Basic Science Grant)
Total Direct Cost: $20,000
Role: Co-Principal Investigator

- **What other organizations were involved as partners?**

Organization Name: Theratechnologies

Location of Organization: *Quebec, Canada*

Partner's contribution to the project: Material support (future); This company will provide the study drug and placebo, as previously described. During this reporting period, we were able to secure a material transfer agreement with Theratechnologies for this arrangement.

Organization Name: Union Memorial Hospital

Location of Organization: *Baltimore, MD*

Partner's contribution to the project: Collaboration in research, study set-up

Organization Name: University of Maryland/Shock Trauma

Location of Organization: *Baltimore, MD*

Partner's contribution to the project: Collaboration in research, study set-up

Organization Name: Walter Reed NMMC

Location of Organization: *Bethesda, MD*

Partner's contribution to the project: Collaboration in research, study set-up

8. **SPECIAL REPORTING REQUIREMENTS**

- **COLLABORATIVE AWARDS:** Our collaborating institutions (Union Memorial Hospital, University of Maryland, and Walter Reed) have been involved with study set up, including protocol development and submitting regulatory documents (ie-IRB exemption). These contributions are denoted above under 'Accomplishments'.
- **QUAD CHARTS:** Attached

9. **APPENDICES:**

Dr. Jaimie T. Shores
Associate Professor

Department of Plastic and Reconstructive Surgery

601 North Caroline St, Suite 8161
Baltimore, Maryland 21287
443-287- 6012 Office

JOHNS HOPKINS
MEDICINE

September 20, 2017

Mr. Lance Nowell
Tunnell Government Services in support of the Congressionally Directed Medical Research Programs (CDMRP)
U.S. Army Medical Research & Materiel Command
Fort Detrick, MD

Re: Request for Re-allocation of Funds
W81XWH-16-C-0188
"Tesamorelin Therapy to Enhance Axonal Regeneration, Minimize Muscle Atrophy and Improve Functional Outcomes Following Peripheral Nerve Injury and Repair"

Dear Mr. Nowell,

We are respectfully requesting a re-allocation of funds for the above referenced project.

As described in the Technical Report submitted in July, there were significant delays related to IRB approval as well as staffing delays. I have attached a revised SF424 Budget with the revised current budgetary for your review. In addition, please note the following to provide a detailed explanation for the request.

Requests for Budget Adjustments:

1) Elimination of Study Nurse position:

In the budget, there is funding to support 20% effort of a study nurse. Initially, it was thought that this position would be needed for collection of blood samples, vitals, and patient education regarding drug administration. However, it later became clear that blood sample collection would be included in laboratory costs and an intake nurse would be provided with facility fees during each follow up appointment. The investigational drug services pharmacy at Hopkins will provide education regarding drug administration. Issues related to drug administration will be handled by the study team at follow up appointments. For these reasons, the study nurse position is redundant and can be eliminated.

2) Study Coordinator Salary Adjustment:

We have hired Ala Elhelali as our study coordinator. She is defending her PhD thesis this month (August) and will begin work on October 5, 2017. Given her desire for academic advancement, her position has been structured as a post-doctoral fellowship. Her job description will not differ from what was originally described. The salary at JHU for a post-doctoral fellow is $47,844 (fringe benefits- $9,234).

3) Modification of Post-Doctoral Associate Position to Sr. Research Technician:

The budget currently includes funding for a Post-Doctoral Associate (40% effort) to assist with data collection and management, patient coordination, and administrative tasks. We request that this position be re-titled Senior Research Technician with 50% effort. We hired a well-qualified applicant (Chia Na Min) with a Master's degree and extensive experience, but she could not be hired as a post-doctoral fellow as she does not have a doctoral degree. Her job description will not differ from was originally described. The base salary for this position is currently listed as $60,572 (fringe $11,690). However, Ms. Min was hired

with a base salary of $44,325 (fringe $15,071). At 50% effort, requested salary support is $26,595 (fringe $9,043). She is to begin her position in October, 2017.

4) Increased Percent Effort for W.P. Andrew Lee, MD (Co-PI):

Dr. Lee's percent effort is currently listed as 1% FTE. However, the percent effort required of Dr. Lee has been significantly greater. In addition to his efforts with regards to study protocol development, Dr. Lee has also been very active in interviewing and hiring applicants and providing input and assistance with clearing regulatory and administrative hurdles. Dr. Lee's actual percent effort is estimated to be 5% effort. At 5% effort, requested salary support is $37,175 (fringe $12,640).

5) Re-Allocation of Funds from Year 1 to Later Years:

Initiation of patient recruitment has been delayed to unexpected delays in IRB clearance and personnel hires. Despite these delays, significant progress has been made in clearing regulatory hurdles (IND exemption granted, JHU IRB approved, Study Coordinator and Senior Research Technician to begin working next month).

Given the delays in patient recruitment, much of the funding anticipated to be required in Year 1 was not spent, and we now anticipate that these funds will be needed in later years to complete the study as described.

We therefore request that the unused funds from Year 1 be rolled over for use in later years.

Yours truly,

Jaimie T. Shores, MD

Tesamorelin therapy to enhance axonal regeneration, minimize muscle atrophy and improve functional outcomes following nerve injury and repair

DM153184

W81XWH-16-C-0188

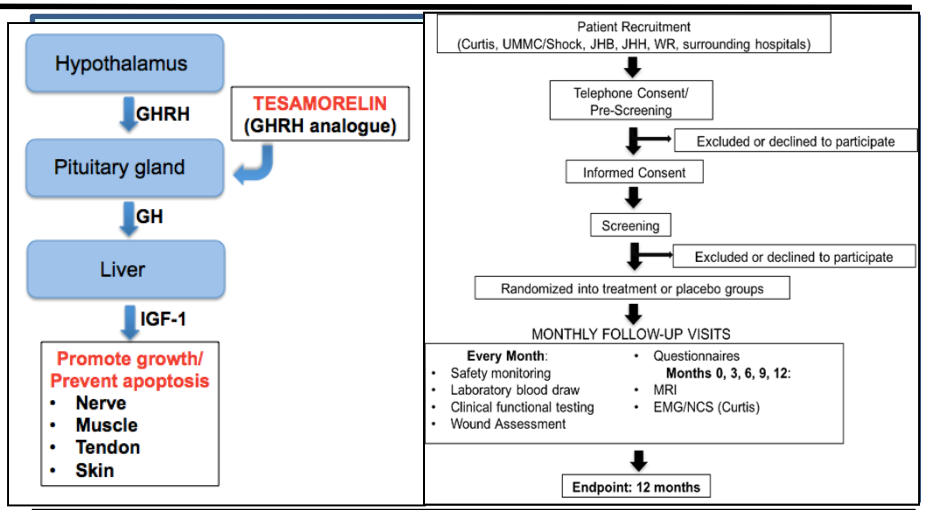
PI: Jaimie Shores, M.D. **Org:** Johns Hopkins University School of Medicine **Award Amount:** $2,926,762

Study Aims

- Specific Aim 1: Test efficacy of tesamorelin as a therapy to enhance axonal regeneration, minimize muscle atrophy and improve functional outcomes following peripheral nerve injury.
- Specific Aim 2: Confirm safety of tesamorelin treatment
- Specific Aim 3: Assess potential secondary benefits of tesamorelin treatment from wound and tendon healing
- Specific Aim 4: Prospectively validate MRI tractography as diagnostic/prognostic tool for peripheral nerve injury

Approach

Multi-institutional Phase II clinical trial comparing tesamorelin treatment to placebo. Military and civilian adult patients with ulnar nerve injuries repaired primarily will be enrolled. Endpoint will be one year. Outcome measures will include EMG/NCS, MRI, clinical functional assessments, and patient questionnaires.



Left: Tesamorelin mechanism of action
Right: Study flow chart

Timeline and Cost

Activities	CY 17	18	19	20
Regulatory approval and study set-up				
Recruit, screen, enroll 36 patients				
Patient follow up, testing, monitoring				
Final data collection, analysis				
Estimated Budget ($K)	**$200**	**$850**	**$850**	**$600**

Updated: 7/1517

Goals/Milestones

CY17 Goal – Study set-up, initiation
☑ Secure IND, IRB, (HRPO pending)
☑ Hire study coordinator and research tech
☐ Begin recruiting patients
☐ Patient follow up, testing, monitoring

CY18 Goals – Study continuation
☐ Continue recruiting patients
☐ Patient follow up, testing, monitoring

CY19 Goal – Study continuation
☐ Final patient recruitment
☐ Patient follow up, testing, monitoring

CY20 Goal – Study wrap-up
☐ Final patient follow up, testing, monitoring
☐ Final data collection, final analysis

Comments/Challenges/Issues/Concerns

- Completion of study set up delayed but nearly complete (pending HRPO approval)
- Actual spending less than projected because of delay in patient recruitment

Budget Expenditure to Date

Projected Expenditure: $191,100
Actual Expenditure: $76,044